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AN INQUIRY INTO THE ETIOLOGY OF CANCER.

WITH SOME REFERENCE TO THE LATEST INVESTIGATIONS OF THE ITALIAN PATHOLOGISTS.[1]

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THE subject of the etiology of tumors, benign and malignant, seems to me the most important and, at the same time, vexed problem now before the surgical pathologists of the world. The universality of their distribution, their general prevalence, their horrible malignancy, and the futility of all save operative methods of treatment, combine to make cancers the most dreaded, because the least understood enemies of the human race.

To attack this problem successfully, pathologists of the future must begin by studying tumor-formation in the vegetable world before studying it in animals—*i. e.*, the comparative method of investigation must be adopted.

Xylomata, or woody tumors, are so exceedingly common that they have failed to attract the attention which they deserve. A large proportion of these growths in trees and shrubs are of parasitic origin; the rest of them are undoubtedly due to disturbance or injury, such as follow traumatic or external irritation. A careful study of them will lend great aid in attacking the problem in its highest phases. Nevertheless, this is not the place to go into details of this description. It may not be amiss, however, to point out the great benefit that would accrue from a combination of botanists, zoologists, veterinarians, and our own profession, for the purposes of mutual aid in this matter.

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[1] A report submitted to the American Surgical Association, April, 1898, by the Chairman of the Committee on the Nomenclature and Study of Tumors.

In submitting the following paper as coming from the Committee on Nomenclature and Study of Tumors, I wish, first of all, to assume the responsibility for any opinions therein expressed. The other members of the committee have kindly permitted me to present this communication as a report, in which, nevertheless, they have not taken personal part.

Much reason as there is to consider malignant disease as in all probability an expression of infection, it will be worth while to devote a little time to the consideration of the causes of the more common benign tumors.

The *lipomata* are the most frequently met with of all, and must find their explanation in some disturbance of nutrition due to faulty innervation. This is easily explained, since they are usually of traumatic origin. The injury has usually been so slight and so long past as to be forgotten. Lipomata are frequently multiple, and then usually symmetrically placed, and such distribution can be explained only through the agency of the nervous system.

Fibromata, also, are usually of traumatic origin, and, if careful investigation be made, the majority will be found to contain minute foreign bodies, such as slivers, splinters, etc., which have served as the exciting cause, and which give these growths a strong resemblance to many of the xylomata already referred to. This is especially true of those fibrous tumors found about the hands and feet.

Myofibroma of the uterus, which is, strictly speaking, leiomyoma, has been of late regarded as of parasitic origin. Without placing great reliance upon the discovery, recently reported, of actual parasites, it is worth while, at least, to remember that some years ago Billroth made a careful study of these growths, and found that they always commenced by formation around a small bloodvessel. If, now, this be true we are compelled to view such neoplasms as due to something circulating through the bloodvessels—*i. e.*, carried by the blood current, and, consequently, necessarily parasitic.

Chondroma is by all means most common in infancy and childhood, and its consideration is practically inseparable from that of rickets. Such cartilaginous tumors as are not to be explained as expressions of rhachitis are to be regarded as inclusions, according to the embryonal theory of Cohnheim.

Osteoma is, for the most part, to be explained on embryonal grounds (Cohnheim). It is often seen as an exostosis in the neighborhood of an epiphysis, or as an ossification of some cartilaginous " rest;" in many other cases it is the result of traumatic osteoperiostitis, or of syphilis or rhachitis.

Adenoma is the nearest approach to a malignant tumor which is consistent with a non-parasitic theory, and every surgeon knows how frequently an adenoma becomes converted into carcinoma. It requires only the added impetus of a parasite to convert an innocent enlargement into an exceedingly malignant growth.

When now we come to *malignant tumors*, the only two theories which are at all worth consideration are the embryonal and the parasitic. All others are either secondary or subsidiary and included in one of the above. Thus the influence which trauma, previous inflammation, diet, surroundings, etc., may exert is to be regarded just as one would regard the same things in predisposing to or permitting tubercular or pyogenic infection.

The evolutionist's view of cancer is not, necessarily, that of the comparative pathologist, although they cannot vary much. If we accept, for instance, Williams's definition of cancer as "The expression of an indefinitely sustained power of certain cells to grow and multiply in excess of normal requirements," we have one which will apply to tumors either in vegetables, trees, or animals.

In the vegetable kingdom, it is hard to draw a distinction between various grades of malignancy. Nevertheless, that tumors kill a large proportion of trees and shrubs will not be disputed by those who have studied the subject. While the method of death in plants or animals is essentially the same—*i. e.*, through ulceration, starvation, and toxic action—the fact that diet cuts some figure among animals in this regard has been shown by Rayer, who found that carnivorous animals are more prone to cancer than herbivorous, just the reverse being the case concerning tuberculosis.

The evolutionists have shown us that an adult cell has a power of relapsing to an earlier or primitive condition, and thus may commence the neoplastic process. Thus cancers, as well as certain processes of repair, are by some regarded as reversions. The embryologists have also shown us that little particles, or foci, of embryonal cells may become imbedded in adult tissue, still retaining their primitive or unspecialized characteristics with their accompanying powers of independent growth.

The rapid multiplication of muscle-fibres in the uterus during pregnancy, or of the heart in hypertrophy, or of the connective-tissue corpuscles in healing wounds has shown us that cells of all descriptions possess remarkable reproductive powers in the presence of proper stimuli. In a genuine hypertrophy the new cells are a perfect type of their ancestors, and, as such, are true to the organism. Among benign tumors these new cells form by cellular division, and are of no utility to the organism. Imperfectly bred new cells may be of value to the body, as in cicatricial tissue; but the cells which have fallen from the first estate of their ancestors and are of a lower grade of vitality, and have become hostile to the organism, are those seen in sarcoma and carcinoma. This is the briefest and best epitome of the evolutionist's view of cancer.

Cancer has been also happily defined as an abortive attempt of gland epithelium to reproduce itself, in which respect it is a constant parody on true gland tissue. Sarcoma is a similar process pertaining to mesoblastic cells. It must now be asked, Can this failure in cell-breeding be accounted for only by a tendency to reversion, or only by the invasion of parasites, or by the occasionally inevitable combination of both? The evolutionist will insist that his view is correct, and that a parasitic feature, if present, must be accidental and secondary. In doing this he will claim that the essential, predisposing cause of cancer is senility—in other words, that, just as soon as the food supply begins to fail, liability to cancer begins, and that such malnutrition may result either from functional senility, or atrophy and instability, due to ancestral and reversionary tendencies. Thus, in the mamma and uterus, when function ceases such malnutritional changes commence. In the lips and tongue atrophic alterations are largely due to loss of teeth; while at the pylorus, the old gizzard region, we have a very common site for cancer. Or, to sum this up, just so soon as an organ or tissue begins to fail of nutrition, it is apt to begin preying on its own kind, like a plant running to seed in poor soil, in a desperate endeavor to hold its own, which, as Jonathan Hutchinson has termed it, is, in fact, a *rebellion of the cells*; and which, as his nephew, Woods Hutchinson, puts it, is, like many another rebellion, chiefly provoked by starvation and want.

Fascinating as is this view, it is, nevertheless, quite insufficient for our purpose. We used to be taught that cancer was exceedingly prevalent at certain ages, and perhaps this statement is correct when one sees but few instances of this trouble. For myself, however, living in a region where cancer is exceedingly prevalent, I have to witness the ravages of this disease in many relatively young people who are far below the supposititious cancer age; and the average practitioner who fails to recognize a malignant growth, merely because he finds it in a young person, is as sadly misled by old statements as is he who makes the same mistake because the patient did not complain of lancinating pains.

There are certain clinical considerations pertaining to the study of cancer which can hardly be omitted in a paper of this general scope.

(*a*) Influence of *sex*. Williams found, for instance, that for every 100 males dying of cancer, 223 females perished from the same disease. Of late years this disproportion has somewhat diminished; nevertheless, women are still more subject to malignant growths. Of cancer in women the breast is involved in 40 per cent., the uterus in 34 per cent., while the rest of the body furnishes the other 26 per cent. In males the parts about the mouth yield about 40 per cent. of the cases. Out of 1878 consecutive cases of cancer of the breast in both sexes the male mamma was involved in only sixteen instances. This discrepancy between the sexes holds good mainly with regard to carcinoma, sex displaying but little difference in regard to liability to sarcoma.

(*b*) The most prolific cancer-producing *age* is that between the fifty-fifth and sixty-fifth years of life—*i. e.*, at a time when the various organs are less active. With the period of tissue and organic maturity, the liability to cancer begins and increases until about the sixtieth year. That the uterus and breast are commonly attacked at an earlier age than other organs is due to their having become *passé* with the conclusion of child-bearing life. With the waning of developmental activities the danger of cancer increases, subsiding only when the organs have undergone complete atrophy. This is true of all known infections, whether cancer be one or not.

(*c*) Williams' careful studies have shown that, at least among females, there is a greater liability to cancer in *brunettes* than in blondes: although the blonde type prevails generally among the population, he found the disease was twice as frequent in brunettes as in blondes. Beddoe furthermore states that red-haired individuals are the most exempt of all. From our own census reports it appears that cancer is twice as frequent among whites as among blacks.

(*d*) *Heredity* of cancer is one of the most vexed questions regarding the dread disease. A family history of cancer will be obtained in from 25 to 35 per cent. of the cases; nevertheless, we must hold that not the disease but only the liability to it can be transmitted from parent to offspring. Even were the disease strictly hereditary, we should find a striking disproportion between it and congenital deformities or defects, or supernumerary organs, which are not transmitted from parent to offspring in anything like 25 per cent. of instances. While a history of multiple instances of cancer in the same family is extremely suggestive, it remains yet to be determined to what extent environment or infection from common sources may account for it. In other words, a notable family history of cancer is, of itself, rather an argument for the parasitic nature of the disease; while the so-called cancer houses have been more or less carefully studied by a London commission.

If cancer is transmitted by heredity it should tend to die out in the course of transmission, as do all abnormalities. Thus, Buxton found that out of 300 marriages in which both husbands and wives were deaf and dumb, the offspring were similarly affected in only 5 per cent. of cases, while of deaf mutes married to those that could hear the proportion of affected offspring was only about two-thirds of one per cent. Williams' two reported instances in which both parents were cancerous, who produced seven children, of whom two had the disease, as well as his collection of seven marriages in which only one parent was cancerous, from which resulted sixty-two children, of whom ten had the disease, are extremely important, although we are not able yet correctly to interpret their entire significance. In this connection, also, there is Broca's celebrated report of the twenty-six descendants of cancerous parents who had attained or exceeded the age of fifty years, of whom fifteen died of the disease.

Williams further concludes that a large proportion of cancer patients are the surviving members of tubercular families; as also, that among families in which cancer prevails there is unusual fecundity, the children averaging four and six-tenths in healthy families, whereas in cancerous families they average eight and eight-tenths to each. Cancer appears to prevail in those who are subject to hypernutrition, this being true even of the survivors of tubercular families.

(*e*) Beneke has described cancer patients as having large hearts and arteries and small lungs; whereas in tuberculosis we have to do with small hearts and large lungs. Beneke also noted that cancers are rare in prisons, where animal food is not freely furnished and where work is hard. Nevertheless, vegetarians are by no means exempt.

(*f*) There can be no doubt that cancer is upon the increase. In 1840, in England, the proportion of deaths from cancer, as compared with the total mortality, was 1 in 129; in 1880 this had risen to 1 in 28. Williams estimated a few years ago that at least 40,000 persons were suffering from cancer in England and Wales; this augmented cancer mortality rate became conspicuous, notwithstanding great improvement in the general sanitary condition. In 1861 there were in England 376 deaths from cancer to the million of population. Twenty-five years later there were 610, and this at a time when the death-rate from phthisis had notably diminished. There can be no doubt that the proportion of this increased death-rate may be in part accounted for by more accurate diagnosis; nevertheless, the death-rate is unquestionably double what it was twenty or thirty years ago.

From the maps of the United States Census Bureau, as well as from various sources, I have learned that Buffalo, N. Y., is near the centre of an area some two hundred miles in radius where the death-rate from cancer is larger than in any other part of the United States. So prevalent is the disease with us that I have often made the remark that it is we who live in the "Tropic of Cancer."

From the returns of the New York State Board of Health during the ten years from 1885 to 1895 I find that there have been reported 30,692 deaths from cancer. In 1885 there were 1882; in 1890 there were 2878; and in 1895 there were 3454. In other words, in the last year of this decade the total number of deaths from cancer was twice that of its first year. It would seem to me, then, that I certainly have a right to assert that the disease is increasing in frequency.

When Haviland published, in 1892, his *Geographical Description of Heart Disease, Cancer, and Phthisis for England and Wales*, he maintained that cancer is most prevalent in countries traversed by rivers, especially those which flood it; and less prevalent in mountain regions or where floods do not occur. Thus, he finds that the river Thames runs through a vast cancer field, save only where the chalk crops out. But Williams would explain the prevalence of the disease in the Thames Valley by the conditions of life peculiar to its population. He claims that cancer mortality is lowest where the stuggle for existence is hardest, the population densest, the average duration of life shortest, and where the death-rate from tuberculosis is highest—*i. e.*, among the working classes; and that cancer mortality is greatest where the general standard of living is higher and life more easily maintained.

Much, also, of interest can be gleaned from the researches of Noel, which go to show a certain relation between arboreal cancers and those of man; that is, not only the frequency of malignant tumors in habitations surrounded by or near woods, but the relatively large mortality from cancer among those persons whose occupation obliges them to live amid these surroundings. The statistics of Julliard, Bierry, and Fiessinger, as well as his own, show that excise officers, who in certain parts of the country pass most of their time in isolated paths through woods, are very prone to cancer, as well as those country laborers who work in the woods. For instance, at Lyons, cancer of the lip is said not to exist; rather, all those who go there to be operated upon for this lesion come from the fields.

Cancer-bearing trees are not only exceedingly prevalent in woods and orchards, but it would seem that this plant lesion is contagious, many of them being found in the same neighborhood. Cancer seems to be most frequent in individuals living in isolated houses on the wooded banks of rivers. Insects, as Morau has experimentally shown, and especially the large wasps found in woods, seem to have a decided predilection for arboreal cancer, and may not only carry the infective material from one tree to another, but deposit it in human food. On these insects both protozoa and fungi abound. Hence the question may arise, Can cancer be disseminated through the agency of such insects, or can water, especially in the neighborhood of woods, act as a medium of transport? If the disease be conveyed in food, cancer of the alimentary tract will be the result; if by the finger or skin, any external portions of the body may be affected. The common solitariness of cancer infection in man is often emphasized as an argument against the parasitic theory, but it is now universally conceded that cancer may originate by multiple foci, and that general carcinomatosis and sarcomatosis correspond perfectly to miliary tuberculosis.

Hitherto inoculation experiments, at least in man, as well as for the most part upon the lower animals, have failed. There are a few apparently authentic instances of transmission to the husband from cancer of the uterus. There is also much reason to think that about the mouth and perineum, where the mucous surfaces lie closely in contact, the disease may be spread from one part to another.

Experimental auto-inoculations have practically failed. In 1885 Morau reported inoculation of fragments from an epithelial cancer of a white mouse into ten other mice of the same species, with formation of cancer nodules in eight; which nodules were successfully used for further inoculation in yet other mice. More than this, he placed healthy mice in cages over a pan containing turpentine and camphor, by which they were kept free from insects and remained in perfect health. In other cages he placed white mice with bedbugs taken from the cages of cancerous mice, and observed after a few months that all of the animals infested by these insects were suffering from cancer.

In view, therefore, of all these clinical considerations the balance of this communication will be devoted to a consideration of the parasitic theory of cancer, and may, perhaps, be well prefaced by comparisons between cancer as we know it clinically and certain other universally acknowledged local and general infections. No safe inference can be drawn for or against the infectious nature of a given malady which is based solely upon a time limit. We have some infections, like those of bubonic plague, cholera, etc., which kill within a few hours, and thus present the most acute and distressing types of parasitic infection. There are others which require a few days, as tetanus, pneumonia, meningitis, and the like. There are yet others where the natural course of the disease takes one over a few weeks, such as typhoid fever. In yet others the disease requires at least a few months in which to run its course, as, for example, tuberculosis, save in exceptional instances. Syphilis and leprosy require ordinarily a few years before they would kill through their own ravages.

Thus it will be seen that there are time variations within the widest possible limits, and one does no violence to the theory of parasitism if he accept the view that the infection which shall produce cancer may take a number of years to run its complete course.

Studying now, for a moment, the subject from an historical standpoint, let us, with Roncali, divide the past few years, during which any careful observations have been made, into four periods, as follows:

1. PERIOD OF INACCURATE OBSERVATION AND ERRONEOUS CONCLUSIONS. This begins with Nepveau, who in the year 1872 found microbes in epitheliomata. In 1886 Rappin, Scheurlen, Fraenkel, and others discovered cocci or other bacteria in malignant growths. In 1887 Scheurlen claimed to have discovered a specific organism, but his mistake was soon demonstrated. Besides Scheurlen, Ferrero, Schill, Perrin, Bernabei, Landerer, Maffucci, Babes, Kubassoff, Shattuck and Bal-

lance, as well as many others, recognized microbes in cancerous lesions, but failed to demonstrate their specificity.

2. PERIOD OF ACCURATE OBSERVATION AND INACCURATE CONCLUSIONS. This is essentially the coccidial period. It began with the discovery, by Halle, Virchow, and Gubler, of protozoa in human tumors. These were subsequently assigned to the class of coccidia by a number of observers, among whom the names of Rivolta, Podwyssotzky, and Lindermann are best known. All of these observers became enthusiastic over, but were misled by, the well-known coccidiosis of the rabbit's liver. But there can be no doubt that the observers herewith mentioned observed parasites within and around cancer cells, though they were misled as to their nature. The most prominent of these investigators were D'Arcy Power, Fabre-Domergue, Duplay, Cazin, Török, Unna, Cornil, Kiener, Stroebe, Hlava, Obrzut, Pianese, Darier, Albarran, Malassez, Sjobring, Bouchard, Clarke, Kahane, Foà, Soudakewitsch, Podwyssotzky, Sawtschenko, Ruffer, Walker, and Vedeler. Of the correctness of their observations, at least in most cases, there can be no doubt; their mistake was in the interpretation of the phenomena. Nevertheless, the cell inclusions which they described were challenged by many other observers, who interpreted the phenomena in various ways.

Malassez regarded them as due to fatty degeneration; Török, Unna, and others spoke of colloid degeneration; corneous degeneration was held by Kiener, Domergue, and Petersen; mucoid degeneration was claimed by Hlava and Obrzut; Cornil and Kiener claimed a degeneration of nuclei in polynuclear cells; Virchow held to an endogenous degeneration; D'Arcy Power regarded them as abortive karyokinetic formations which had undergone a peculiar hydropic degeneration; while functional chromatolysis or other aberrent mitotic formations, or irregular vacuolization, as well as a great variety of other changes, were insisted on by various other students. This endless variety of opinion was of itself conclusive proof that the truth had not yet been reached. Moreover, culture experiments were complete failures.

3. ICONOCLASTIC PERIOD OF DOUBT AS TO THE ACCURACY OF ALL PAST RESEARCHES. This period began with Russell's work in 1890, and concluded with the researches of Banti and Nisser in 1894. Thus, Russell described certain round, homogeneous, structureless bodies which he found in groups within the tissues, as well as within the cells, and which he regarded as fungi. Banti found the same objects in Paget's disease, and Nisser isolated from the blood of cancer patients certain blastomycetæ, which he considered to be the actual parasites of cancer

4. PERIOD OF SUCCESSFUL INOCULATION, PRACTISED FOR THE MOST PART BY ITALIAN PATHOLOGISTS. The work of the Italians in this direction has been most creditable and apparently most convincing. It

has been done for the most part by Prof. Sanfelice, of the University of Cagliari, in Sardinia, and Prof. Roncali, of the University Surgical Clinic in Rome. The former published his first paper on the subject in January, 1895, and the latter followed with his first only a month later. To these two men and their assistants we owe most of that which I shall epitomize below.

As the work of these Italians points, with a high degree of probability, toward the blastomycetæ as the active agents, it will be worth while to stop for a moment and rehearse the most important facts known with regard to this class of fungi. It is best known as that to which the common yeast forms belong. These fungi reproduce themselves, not by division into halves, as do the common bacteria, but by the process of budding; the cells, when undergoing this process, appearing under the lens much like the common forms of cacti. Each bud provides itself with a membrane when separating from the parent cell, and thus becomes complete in itself. The parent cell does not die in this process, but gives rise to other buds, the entire process consuming about two hours in those forms where the life-history can be easily watched. This is slower cell division than occurs with the ordinary bacteria. The new cells thus produced are often bound together in clusters or irregular chains. Each cell has its proper membrane, which is filled with protoplasm, and contains a nucleus. It will average eight to ten millimetres in size. Under particularly favorable circumstances spore-formation may also take place, so that from two to ten endospores may be seen in one parent cell. These spores are less resistant than those of the common bacteria. They are killed by five minutes' exposure to 62°–70° C. Those blastomycetæ which are capable of spore-formation are the least hardy, living in the ground for about a year, while others can live, under the same conditions, for three years. This is worth remembering, because there is much reason to think that these fungi are introduced into the system from the most common sources and by the ordinary paths of infection.

They will grow on media which are slightly or strongly acid, and by this means can be separated from many of the common bacteria. Each species has its own peculiarity as to behavior respecting the various sugars. For example, by an ordinary wine yeast 1000 grammes of grape sugar were split up into 506 grammes of alcohol and 30 grammes of other products, including 21 grammes of glycerin. (By the way, the taste of various wines is quite perceptibly influenced by the amount of glycerin present therein.) Alcoholic fermentation can go on with or without access of air. If air be present cell reproduction is more active, and other cell activity is lessened, and vice versa. Acetic fermentation must be aërobic, butyric must be anaërobic; lactic fermentation and putrefaction are faculative aërobic actions.

So far as pathogenic activities are concerned, blastomycetæ are known to be active disease-agents in certain cases. They are commonly found in the urine of diabetic patients, but whether by accident or in some other relation is not positively known. Numerous forms have been cultivated and inoculated, with resulting severe or even fatal symptoms—as in the morbid condition called saccharomycosis, which is known as an experimental disease. Thus it is established that a general infection from this cause is possible, and the question may arise whether general carcinomatosis is of this nature.

Now, it is almost exclusively the blastomycetæ with which the Italians have worked, and have produced their remarkable experimental results, for they have found these organisms both within and between and around cancer cells, and have succeeded in making cultures in and upon acid media. Moreover, by inoculations with these cultures they have produced tumors in animals which bear the strongest possible resemblance to those neoplasms from which the cultures were originally made.

These parasites must be sought for in the periphery of the tumors and in the juices of the same, but not in the central portions, for here they often seem to have disappeared. This is true both of sections for microscopic examination and of the portions which are taken for inoculation purposes. Furthermore, most of the experimental tumors thus produced have returned the same blastomycetæ upon further culture tests. Two or three different forms have been definitely named by their discoverers; thus Sanfelice has described a saccharomycis lithogenes, and Roncali a blastomycis vitro-simile degenerans. These names both call attention to the remarkable properties which some of these fungi possess, not only of undergoing a rapid degeneration, but of displaying a peculiar calcareous deposit within the cell membrane, which is undoubtedly due to calcium carbonate, since when these are treated with 4 per cent. solution of hydrochloric acid the degeneration forms all disappear, while when treated with 4 per cent. sulphuric acid crystals of calcium sulphate form. As showing also their marked tendency toward degeneration, Roncali placed two pieces of tumor in a Petri capsule, and kept it at 37° C. for four days. In the juices the undegenerated forms were undoubtedly much more abundant than in the fresh specimens, which would indicate their truly parasitic nature.

As an illustration of the method of securing cultures, he prepared in one case sixty tubes of distilled water containing a little sugar and acid; in each of them he placed small bits of tumor cut with a sterilized knife. These were kept at 37° C. for ten days, when surface growths were found upon forty-seven of them, which, when examined in the hanging-drop, were easily recognized as blastomycetæ.

Sanfelice has produced small tumors in numerous of the smaller animals by injection of his saccharomycis above alluded to. It is most interesting also that some of the blastomycetæ which he discovered in tumors were identical with those found upon the common lemon, which grows so abundantly upon Italian soil. Among other experiments, he injected the saccharomycis into the mammary gland of a bitch, which lived for fourteen months and then died with a definite tumor in the gland and with metastases in various organs. Also, after injecting this culture into the abdomens of guinea-pigs he saw them die in from twenty to forty days as the result of neoplastic lesions, while when injected beneath the skin they killed the animals in from thirty to fifty days, with local manifestations.

Thus, without quoting in detail the experimental labors of Sanfelice, Roncali, and their pupils, it may be stated as positively proven that the blastomycetæ above alluded to—*i. e.*, at least some of them—are capable, first, of being isolated by culture methods from certain carcinomata and sarcomata; second, of identification as belonging among the yeasts; third, of producing tumors in animals by injection under suitable precautions, the resulting tumors being strikingly analogous to or identical with those from which the cultures were made; and, fourth, of furnishing from these tumors further cultures, from which yet other experimental inoculations can be made.

Without going so far as to say that this can be done in every instance, or that all cancers are necessarily of parasitic origin, one is justified by these results in at least maintaining that some cancers are positively of such origin. If, upon this experimental ground, one should infer that all cancers are parasitic manifestations, he would do, as will be seen, little violence to the laws of logic.

Certain laboratory methods and precautions must be observed in these studies. The culture media must be distinctly acid in reaction. The blastomycetæ in question will grow in distilled water sufficiently acidified, to which a little sugar has been added, or in any of the ordinary media, provided only that they be sufficiently acid. I suppose that one reason why they have so long eluded detection in these locations is because neutral or alkaline media have been those generally employed. For inoculation, the distilled water above alluded to, or bouillon cultures, may be used with a hypodermic syringe, and the culture injected into a testicle or into the abdomen, or a small quantity of the culture from a solid medium may be inserted beneath the skin after making a small incision.

With these fungi, as with many other organisms, it is necessary often to do something to enhance their virulence before they become markedly pathogenic. Here we take advantage of an artificial symbiosis, and grow them upon the surface of a tetanus culture some eight to ten days old. In this way the desired augmentation of virulence is produced, the tetanus bacilli, being anaërobic, growing in the depths of the medium, while the fresh culture is planted upon its surface. Similar manipulation is often resorted to in the laboratory in connection with bacillus pyocyaneus and bacillus prodigiosus.

When it comes to the detection of these fungi in microscope sections, the methods are more or less complicated, and require considerable training in special manipulation and observation. The directions are as follows:

Pieces of the tumor taken from the margin of the growth, or at least from the outlying portions, are placed for ten minutes in a saturated solution of corrosive sublimate. The addition of a few drops of acetic acid while the pieces are immersed adds to the effect of the sublimate. After removal they are left for twenty-four hours in 60 per cent. alcohol, to which there is added ordinary tincture of iodine to remove the sublimate. It is added gradually until the solution ceases to be decolorized by decomposition. After this the pieces of tumor are hardened in strong alcohol in the usual way, cleared up in xylol, and mounted in paraffin. From these small masses sections are cut as usual.

If one desire to stain the entire mass before cutting the sections, it is placed, after leaving the alcohol, for twenty-fours in lithium carmine, then for twenty-four hours in alcohol containing ½ per cent. of hydrochloric acid. It is then hardened in alcohol and mounted as before.

When now the sections are cut, they are again freed from paraffin with xylol, treated with absolute alcohol, and left for from five to fifteen minutes in Ehrlich's fluid. After this they are washed in distilled water, put for five minutes in ½ per cent. solution of oxalic acid, washed again with distilled water, and then in absolute alcohol until it is no longer discolored. They are now cleared in xylol and mounted in balsam. Prepared in this way, the parasites are of a purple color and the tissue red.

The second method, which we owe to Sanfelice, consists in placing the sections for from ten to sixty minutes, or longer, in the following solution:

Saturated watery solution of safranine	1 part.
Saturated alcoholic solution of malachite green	½ part.
Distilled water	½ part.

They are then washed in distilled water, decolorized by five minutes' immersion in ½ per cent. oxalic solution, washed again in water, then passed through alcohol and xylol and mounted in balsam. Prepared in this way, the parasites take a green or bluish-green color, while the protoplasm is red and the nuclei safranine. Roncali suggests also the following solution:

Saturated watery solution of safranine	5 or 6 parts.
Saturated alcoholic solution of gentian violet	1 part.
Distilled water	3 or 4 parts.

Sections are left from two to four minutes in this fluid, after which they are treated as above. Thus treated, the parasites assume a purple and the tissues a red color. This method has the advantage of saving time, but does not display the parasites to nearly as good advantage.

For much of the above information I am indebted to a personal acquaintance with Professor Roncali, from whom I secured my first cultures and illustrative slides. His writings on the subject have been numerous and are mentioned below.

During a recent visit to Vienna I had also the advantage of noting what was being done in this line of research in the clinic of Professor Gussenbauer. Within the past year or so seven cases of melano-sarcoma have been carefully investigated by one of his assistants, with the result that from every case there has been isolated an anaërobic coccus which grows in ordinary media with a dark color. This color is not that which gives rise to the pigment of the active disease. This latter is due rather to a metamorphosed hæmoglobin which is known as melanine. Nevertheless, the coccus growing *en masse* assumes an almost brown or black color. Sufficient time had not elapsed when I last saw these cultures for experimentation, but it was proposed to inoculate them in horses, which are known to be peculiarly susceptible to melano-sarcoma.

Thus it will be seen that the problem of the nature of cancer, and consequently of its cure, is a most complicated one and must be studied from many sides.

The following list of papers and monographs pertaining to the subjects discussed in the above report is by no means complete, but will be found helpful by those studying the subject.

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A CONTRIBUTION TO OUR KNOWLEDGE OF THE ETIOLOGY OF INFLAMMATIONS OF THE ACCESSORY SINUSES OF THE NOSE.

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During the last year we have examined microscopically and by culture methods the material from eighteen cases of inflammation of the antrum of Highmore and the frontal and ethmoidal sinuses. We have